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Markers of Mitochondrial Mitophagy and Fusion-to-Fission Ratio are Greater in Older vs. Young Rats

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Mitochondrial dysfunction in skeletal muscle can contribute to age-related metabolic and functional declines due to the mitochondria's essential role in energy production, calcium handling, and apoptosis. Skeletal muscle mitochondria form a reticulum and can share membrane potential and matrix content. In healthy mitochondria, this network is maintained by a constant balance between mitochondrial fission, fusion, and mitophagy. Thus, proper regulation of mitochondrial fission, fusion, and mitophagy maintains structure and is crucial for adequate energy production. **PURPOSE:** To determine age-related differences in mitochondrial fusion, fission, and mitophagy in skeletal muscle, as measured by mitofusin 2 (MFN2), fission-1 (Fis1), and Parkin protein expression, respectively. **METHODS:** Six young (≤6 months) and six old (≥18 months) male and female Sprague-Dawley rats were anesthetized, and their tibialis anterior muscles were excised and homogenized. Western blots were used to determine protein expression of MFN2, Fis1 and Parkin. All blots were normalized to total protein in each sample using stain-free blots. Fusion-to-fission ratio was also determined as the ratio of MFN2 to Fis1 expression. Independent t-tests were used to compare protein expression between young and old rats. **RESULTS:** Muscle from old rats had 4-fold greater expression of Parkin compared with young rats (0.130 ± 0.058 vs. 0.033 ± 0.013 AU, respectively; P = 0.003). Fis1 expression did not differ between groups (P = 0.63), but MFN2 tended to be higher in old rats (0.055 ± 0.022 vs. 0.033 ± 0.012 AU; P = 0.06). The fusion-to-fission ratio was 49% higher in the old vs. young rats (0.725 ± 0.226 vs. 0.487 ± 0.125; P = 0.04). **CONCLUSION:** Collectively, our results suggest that mitochondrial mitophagy and fusion both increase in skeletal muscle with age. Although Fis1, as a marker of mitochondrial fission, was not different with age, the greater ratio of MFN2 to Fis1 indicated a shift favoring increased relative fusion. This may serve as a compensatory mechanism for dysfunctional mitochondria to preserve membrane potential and share matrix contents. Therefore, the relative ratio of fusion to fission may be a greater determinant of mitochondrial dysfunction in older individuals.

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